Clinical Medicine

Clinical Evaluation and Use of Urine Screening for Drug Abuse

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Urine drug screening is indicated to evaluate patients who show mental status or behavioral changes and to monitor the abstinence of drug abusers. The appropriate timing for collecting urine specimens may vary depending on the suspected drug of abuse and on laboratory factors. Laboratories use a variety of techniques to do urine screens, and these must be understood by clinicians ordering the screens to interpret results correctly. In treating drug-abusing patients, clinicians must apply structured reinforcement in conjunction with urine screen results to aid patients in achieving abstinence.

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Recently there has been a dramatic increase in the frequency with which urine screening is used to detect drug abuse. Not only physicians possess the prerogative of ordering this type of laboratory examination, but law enforcement officials and employers, among others, have the option as well. In the midst of the current national furor over urine testing, the technical and clinical knowledge essential to make appropriate use of the information supplied by the tests often gets obscured. It remains incumbent on physicians of all specialties who may treat in their practice patients with substance use disorders to comprehend fully all technical and clinical facets of the use of urine screening.

Urine screening is a tripartite procedure involving the collection of specimens, a laboratory analysis, and the clinical application of the laboratory results. After reviewing the indications for doing a urine drug screen, we will examine in detail all three aspects of the procedure. We will offer general guidelines for the use of urine screens that clinicians, particularly primary care providers, can tailor to fit their diagnostic and treatment goals with individual patients in specific situations.

Indications for Urine Screening

Urine drug screens may be ordered for diagnostic or treatment purposes, or both simultaneously. Probably the most common area in which they deserve consideration as a diagnostic tool is in evaluating mental status changes. Even in the elderly, who may not be using illicit drugs, urine screening may uncover an inappropriate use of prescription medications or over-the-counter drugs such as phenylpropanolamine or scopolamine hydrobromide as causative factors in delirium, dementia, or depression.[1] Similarly, urine screening should be done for all adolescents or young adults who present with school difficulties, behavior problems, or unexplained medical problems to rule out drug abuse as an etiologic concern.[2] Other indications for the diagnostic use of urine screens include a newly developing psychosis, an unexpected deterioration in occupational or social functioning, and, of course, to identify the specific substance a known drug abuser has taken.

Using urine screening in the workplace to detect psychoactive substance use remains a hotly controversial issue. The federal government has initiated a program for some of its employees to screen for the use of marijuana, cocaine, amphetamines, opiates, and phencyclidine. It involves the nonobserved collection of specimens and does not screen for alcohol or prescription drug use. Exponents of the plan contend that the procedure will cost $15 to $25 per specimen, while critics insist that proper testing might actually run from $100 to $300 per specimen. Furthermore, no published research has yet shown that urine screening enhances workplace safety. Private industries have launched screening programs without any requirement to adhere to legislated guidelines. Extensive litigation is in process that challenges the legality of urine screening. At present, any definitive statement about the value of workplace screening must await a more thorough scientific investigation.[3]

Once urine screens have aided in achieving a diagnosis, they can evolve into a powerful treatment tool. Their optimal potency in treatment relies on a grasp of collection procedures and laboratory techniques.

Collecting Specimens

Central to the actual physical collection of specimens is the obvious though potentially overlooked fact that the act of providing the specimen must be carefully observed by a reliable party from urethra to container. Urine from a source other than the person on whom the screening is being done can easily be substituted, or the specimen can be diluted or adulterated.[4] If direct observation is judged inadvisable, requesting donors to leave coats, other outer garments, and personal belongings outside the collection room can help prevent the substitution of false specimens. The absence of a sink in the collection room and the use of a bluing agent to

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
EIA = enzyme immunoassay
FPIA = fluorescence polarization immunoassay
GC = gas chromatography
HPLC = high-performance liquid chromatography
MS = mass spectrometry
RIA = radioimmunoassay
THC = tetrahydrocannabinol
TLC = thin-layer chromatography

color the toilet water can pose a barrier to diluting a specimen. Collection personnel can inspect the urine color and measure its temperature to verify specimen validity. Laboratory personnel can check the urine pH and specific gravity to discover adulteration or dilution.[5] Immediately after obtaining a filled specimen container, collection personnel must, in view of the donor, affix a label bearing the donor's name or identification number (or both). Locked storage of the specimens to prevent possible tampering and refrigeration at 4°C (39°F) if more than several hours elapse before conveying to the laboratory guarantee the optimal integrity of the specimen.[5] Of course, personnel handling urine specimens should wear disposable rubber gloves and practice adequate hand washing to protect themselves from possible exposure to infectious agents in urine.[6]

A first morning urine specimen, being the most concentrated, represents the ideal specimen. An actual urine drug concentration depends, however, on the dose, the route of administration, the time since administration, and a person's physiologic state,[7(p80)] so scheduling the appropriate frequency of specimen collection remains the more complex issue. In the early 1960s, at the inception of methadone maintenance—the original form of structured drug abuse treatment—urine specimens were collected daily.[8] Limitations of expense and convenience make this theoretically ideal collection schedule unfeasible. Establishing a collection frequency with regard to the specific drugs one hopes to detect, the particular characteristics of a patient, and the types of laboratory tests available—discussed later—supplies a more reasonable approach to this problem. For example, many methadone programs in the 1970s altered their collection schedule to a random once-a-week collection.[9] In this paradigm, patients must give one specimen per week without knowing in advance on which day it will be required. The rationale behind this change relates to recognizing that a serious pattern of opiate use in a primary opiate abuser almost inevitably leads to daily use to prevent physiologic withdrawal.[10] Continuous drug use will not escape exposure by once-per-week screening.

Harford and Kleber also showed that money and time could be saved by implementing screening at random intervals, which offered the ability to detect illicit opiate use in methadone patients superior to that of random weekly screening.[11] In random-interval screening, patients incur an obligation to provide specimens on an average of only two or three times per month as compared with random weekly screening that requires four or more specimens per month. In random-interval screening, however, patients remain at risk to give a specimen on every single day of the month, even potentially on two consecutive days. This feature eliminates the "safe" periods inherent in random weekly screening—the days remaining in a given week after a patient has provided a specimen and knows screening will not occur again until the following week. Thus, in general, greater randomizing of collection schedules enhances the capacity to detect drug use.

In contrast to opiate addicts, primary stimulant abusers often self-administer their drugs in binges with intercurrent periods of abstinence.[10] Cocaine poses a particular problem in conjunction with this phenomenon of binging because of its brief half-life of 40 to 80 minutes.[12] Because the drug and its metabolites are excreted so rapidly, they are present in urine for a relatively short period after the drug is administered. With standard laboratory methods, therefore, urine must be sampled at least two to three times a week to reliably detect cocaine use.[13] Even without randomization, three times per week collection will not likely miss cocaine use. Amphetamines, which have a longer half-life of 6 to 12 hours,[14] may appear in urine for more than two days following their administration.[15] Screening once or twice a week, particularly if done randomly, should prove sufficient.

At the other end of the spectrum lies marijuana. The major psychoactive alkaloid in marijuana, tetrahydrocannabinol (THC), and its metabolites display high lipid solubility and can be present in the body and the urine for more than a week after a single exposure and for as long as four to six weeks after continuous heavy use.[16] In this situation, a urine screen positive for marijuana merely indicates recent use and does not quantify or date the use. To screen for marijuana any more regularly than once or, at most, twice per month simply wastes money. Quantitative blood concentrations may prove more useful in a clinical situation mandating a diagnosis of acute marijuana intoxication.[4]

The benzodiazepines occupy the middle of the continuum. Like THC, benzodiazepines are highly lipid soluble, but different agents have widely varying half-lives and potencies.[17] Longer acting and less powerful drugs on a milligram-for-milligram basis such as diazepam or chlordiazepoxide may appear in urine for more than a week after a single ingestion.[15] Quantities of low-milligram, short-half-life drugs, such as triazolam, sufficient to be detected in urine may disappear after 24 hours or less. In general, then, adequate screening for benzodiazepines can occur weekly or even every two weeks in some cases. Concerns over the

TABLE 1.—*Detection Limits for Urine Drug Testing*

Drug	Dose, mg	Detection Time, hr	Screening Frequency, ×/wk
Amphetamines	30	1 to 120	1 to 2
Barbiturates			
Short-acting	100	At least 4.5‡	1 to 2
Phenobarbital	30	6 to 24	1 to 2
Benzodiazepines			
Long-acting—diazepam	10	7‡	1
Short-acting—triazolam	0.5	24	2 to 3
Cocaine	250	8 to 48	2 to 3
Methadone	40	7.5 to 56	2 to 3
Methaqualone	150	60	1 to 2
Morphine—opiates (IV)	10	84	1
THC metabolites	*	7 to 34‡	§
	†	6 to 81‡	

IV=intravenous administration, THC=tetrahydrocannabinol

*Marijuana use once per week.
†Marijuana use daily.
‡Days.
§Once a month.

abuse of agents with short half-lives, however, should prompt screening several times per week on a random basis. Table 1 summarizes the detection limits and suggested screening frequency for commonly abused drugs.

Laboratory Analysis of Specimens

While effective urine screening depends entirely on laboratory technique, laboratory analysis can be fraught with pitfalls. Reports through the years have shown that many laboratories doing urine screening provide grossly inaccurate results.[18-20] In 1985 the Centers for Disease Control (CDC) did a blind examination of 13 laboratories serving 262 methadone maintenance clinics.[21] They found unacceptably high false-negative rates averaging 59% for barbiturates, 69% for amphetamines, 12% for methadone, 64% for cocaine, and 62% for morphine. Average false-positive rates were not as dismal, but some laboratories did as poorly as 37% false-positive for methadone. The CDC researchers calculate that as much as $75.6 million is wasted annually on erroneous drug testing results. This phenomenon of poor performance can be explained by an understanding of the various laboratory procedures that are used to analyze specimens, the cross-reactions with other prescription or nonprescription medications that can occur, and the uneven quality of performance in each particular laboratory. Knowledge of these factors helps to eliminate much of the disruption that can ensue when practitioners attempt to apply urine screen results clinically.

Laboratories use two types of tests, screening and confirmatory, for detecting drugs in urine. Screening tests, designed to be simple, efficient, inexpensive, and rapid, generally are the initial step carried out on a large number of specimens. Confirmatory tests are reserved for those specimens found positive with the screening test. Confirmatory tests tend to be more complex and labor-intensive than screening tests.

As with all chemical laboratory tests, decisions must be made as to what test values will be considered abnormal or "positive." The threshold concentration, or "cutoff," used in screening tests must be carefully selected to obtain the desired sensitivity and precision. The threshold concentration differs from the sensitivity or detection limit of an assay. This latter value refers to the absolute lowest detectable analyte concentration. Threshold concentrations define the drug level at which specimens will be called positive and are usually set at a level higher than the detection limit of the assay to avoid imprecision that may occur near the detection limit. For example, the cutoff value for a benzodiazepine radioimmunoassay (RIA) can be set at 100 ng per ml, well above its detection limit of 5 ng per ml.[22] Table 2 lists the threshold concentrations for selected drugs, analyzed by three common types of screening assays. The selection of the appropriate cutoff value in a given method will depend on a particular assay's precision and accuracy.

TABLE 2.—*Threshold Concentrations, in μg/ml Urine*

Drug	Enzyme Immunoassay	Radio-immunoassay*	Thin-Layer Chromatography†
Barbiturates	0.3-2.0	0.2-3.4	0.5-1.0
Amphetamines	0.3-1.0	1.0	0.3-0.5
Methadone	0.3	...	0.5
Benzodiazepines	0.3-2.0	0.1	1.0
Propoxyphene hydrochloride	0.3	...	0.5
Phencyclidine	0.08	0.025-0.10	0.1-0.2
Cocaine			
Parent	25.0	0.45	1.0
Benzoylecgonine—cocaine metabolite	0.3	0.3	1.0
Opiates—morphine	0.3	0.3	0.25
Codeine	1.0	0.16	0.25
Cannabinoids—as total metabolites	0.1	0.1	0.075-0.1
Methaqualone	0.3	0.75	1.0

*Abuscreen.
†"Traditional" thin-layer chromatography; sensitivity varies widely, depending on the system used.

A lower working detection limit obviously improves the yield of true-positive tests but also increases the chance of false-positive tests. If the cutoff point is too low, a confirmatory test may not confirm the results of the screening test. Using a higher threshold reduces the incidence of false-positives but increases the likelihood of false-negative results. The choice of a threshold value may also be influenced by the clinical purpose of the test. For example, establishing a threshold value of 100 ng per ml for marijuana screening will minimize the possibility of a positive result for persons with only a passive exposure to cannabis.[23]

Immunoassays

Enzyme immunoassay (EIA), fluorescence polarization immunoassay (FPIA), and RIA are generally preferred for the initial screening. All types of immunoassays depend on the principle of competition between a marked or labeled antigen and an unmarked antigen for binding sites on a specific antibody. For drug detection, the actual drug to be detected serves as the antigen. Therefore, a separate immunoassay procedure must be done for each class of drugs to be detected.

In the enzyme immunoassay system, the marker is an enzyme to which the analyte (drug) molecule has been permanently attached. When the enzyme acts on its substrate in solution, this chemical reaction causes an absorbance change in the solution that can be measured in a spectrophotometer. To carry out the EIA, a sample from a urine specimen that is being checked is placed in a solution along with the substrate and antibodies against a particular drug. At this point, the enzyme-drug complex is added to the solution. If the urine specimen contains none of the drug in question, the antibody will bind to the enzyme-drug complex, rendering the enzyme inactive; the enzyme cannot act on the substrate, and no change in absorbance is noted. Thus, a lack of change in absorbance equates with a negative urine assay.[24] If, however, the urine specimen did contain some of the drug, the drug would bind the antibody to it, preventing the antibody from binding to the enzyme-drug complex; the enzyme would retain activity and the chemical reaction would ensue, in turn causing an increase in light absorbance as measured by the spectrophotometer. In other words, an increase in absorbance means a positive assay.[24]

FPIA assays are based on a similar competitive principle. In this case, the marker is a fluorescein-labeled drug and the system measures the fluorescence polarization resulting from the binding of this tracer to specific antibodies. When more of this marker is bound to antibody—that is, when urine drug concentrations are low—the amount of polarized light emitted will be high because this large complex cannot

tumble freely in solution. When urine drug levels are high, tracer is displaced from the antibody and this small molecule tumbles freely in solution, resulting in less polarized light emitted.[25(p39)]

These immunoassay reagents cost about $1 to $4 per test for each specific drug. Assays have been adapted to several types of batch or random-access analyzers, which allow a large number of specimens to be processed simply and automatically with objective results obtained by the instrument.

Radioimmunoassay, like EIA and FPIA, uses a competitive binding principle but with a radioactive isotope as its marker. The radioactive isotope is bound to a molecule of the drug to be detected and placed in a solution with antibodies to the drug and a specimen of urine. If the urine specimen contains none of the questioned drug, the antibodies will bind to the radioactively labeled drug. Should the urine contain the drug, the free drug will compete with the radioactively labeled drug for antibody binding. In either case the solution undergoes centrifugation until the antigen-antibody complexes precipitate out. After removing the supernatant—a physical separation step not required in EIA or FPIA—a gamma counter measures the radioactivity in the precipitant.[26] The precipitant from a drug-negative specimen will show a high amount of radioactivity because most of the radioactively labeled drug was bound to antibody and precipitated. Conversely, illicit drug, when present, will bind antibody in place of the radioactively labeled drug, and the antigen-antibody complexes that precipitate will show proportionally less radioactivity. Thus, radioactivity counts translate into a quantitative urine drug concentration. Because of the radioactive component, careful monitoring of both personnel and laboratory facilities is required to ensure safe handling, storage, and disposal.

The antibodies used in many immunoassays are not specific for single drugs but cross-react with chemically related drugs and metabolites. For example, the amphetamine EIA will detect not only amphetamine and methamphetamine but also phenylpropanolamine and ephedrine/pseudoephedrine,[27] providing a false-positive result. False-positives may also result from a carryover of a preceding specimen that tested strongly positive.[24]

Thin-layer chromatography (TLC) often functions as an initial screen and, if used appropriately, may also serve to confirm positive immunoassay results. The TLC procedure involves the urine being extracted by an organic solvent, followed by applying of a specimen onto a silica-coated plate. After the plate is immersed in another solvent, various drugs in a sample, depending on their unique solubility, will migrate to different areas of the plate. Spots correlating to the parent drug or its metabolites should appear at a given location on the plate. Small changes in the composition of the developing solvent mixture can result in subtle changes in migration rates. Therefore, reference standards are developed on the same thin-layer plate along with the unknown sample. Spots on the plate from drugs in the unknown specimen can be compared against the standards to aid in identification. Drugs that may migrate to nearby areas can be more precisely identified by immersing the plate in various reagents, which will cause spots representing different drugs to colorize differently, or by examining the plates under ultraviolet light, which allows several drugs to exhibit a characteristic fluorescence.[28]

Advantages of TLC include low cost—about $3 to $4 per specimen to detect all drugs present—and the fact that one test provides a broad screen for a variety of drugs at one time while obviating a reliance on technologically advanced equipment. (A recent research report indicates that EIA reagents may be mixed in a solution simultaneously to provide a comprehensive drug screen like TLC,[29] but this method would require further evaluation before it comes into general use.)

Thin-layer chromatography also has significant disadvantages.[25] It is a labor-intensive and time-consuming technique. It is somewhat subjective because it depends on trained human observers to interpret the visual results. The ability to recognize different metabolite patterns, especially when several drugs are present, requires an experienced technologist. This expertise may vary from laboratory to laboratory or even within laboratories. Occasionally another substance in the urine produces a spot on the chromatogram that either masks or is misinterpreted as the drug in question. Therefore, definitive identification on the basis of a chromogenic reaction, migration, or both, proves impossible.

The proper detection of many benzodiazepines and opiates in urine by TLC—or gas chromatography (GC) or high-performance liquid chromatography (HPLC)—requires a separate hydrolysis step because these drugs are predominantly excreted as their glucuronide metabolites. These metabolites are more polar than the "free" or unconjugated compounds and are not extracted by the organic solvent used in these chromatographic methods. One study graphically shows the importance of this hydrolysis step: 345 urine specimens were tested for opiates by TLC without the hydrolysis step, and also by EIA, which detects the glucuronide metabolites. TLC detected opiates in 95 of the specimens, while EIA found opiates in 200 of the identical specimens.[30]

The stated detection limit for most drugs of abuse analyzed by TLC is approximately 1,000 ng per ml, and TLC generates only qualitative, not quantitative, results. In contrast, EIA systems, because they incorporate a limited set of standards (calibrators), can yield semiquantitative results. Radioimmunoassay and FPIA can be made quantitative because they measure discrete levels along a full standard curve. Many laboratories, however, select a particular threshold level and report results either as positive or negative. For certain drugs, such as cocaine, the immunoassays are more sensitive than TLC. The EIA detection limit for benzoylecgonine, the primary cocaine metabolite, is 300 ng per ml, whereas the detection limit by TLC is 1,000 ng per ml. As a practical example, TLC will detect cocaine metabolites in urine for, at most, 12 to 24 hours after the last use of the drug. Enzyme immunoassay generally detects cocaine for at least 48 hours after its use (Tables 1 and 2).[13]

A confirmatory test—using a more specific method—should be done to verify a positive screening test. Confirmation becomes essential when significant penalties or legal actions will ensue. The confirmatory test ought to be based on a different principle of analysis and be at least as sensitive as the screening test. For example, if the screen were an immunoassay, such as the cannabinoid EIA, the confirmatory technique should use a different methodology—chromatography such as thin-layer, high-performance liquid, or gas—and not another immunoassay such as RIA. The threshold concentration of the confirmatory assay should be set at a concentration consistent with the drug in question,

which may be lower than that used in the preliminary screening. For example, the cannabinoid EIA detects several cannabinoid metabolites and has a threshold of 100 ng per ml; the threshold of the gas chromatography-mass spectrometry (GC-MS) confirmation assay based on the detection of one metabolite, Δ-9-THC-COOH, may be set at 20 ng per ml.[31]

Gas chromatography and high-performance liquid chromatography are used mostly for confirmatory analysis because the procedures are more complex and labor-intensive and do not lend themselves to processing large numbers of specimens. As in TLC, these methods employ a chromatographic separation to allow the identification of unknown drugs in a mixture.[26] In GC a larger volume of urine—5 to 10 ml—is extracted with an organic solvent and the extract is dried down and reconstituted in a small volume of solvent. Minute quantities are then injected into fused silica capillary columns 0.2 to 0.7 mm in diameter and 5 to 100 m in length. The separation results from an equilibrium established between the drug in the mobile or gas phase and drug in the stationary or liquid phase adsorbed on the wall of the column. A differential partition of the drug in these two phases occurs, such that certain drugs will be retained longer than others on the column. A detector observes when the drug emerges from the column, and this retention time helps to identify the drug. The time required to elute any given drug from a GC or HPLC column is not necessarily unique, however, so no single system will suffice for proper drug identification. That is, the retention time alone cannot make a definitive drug identification, and other tests—such as the immunoassay screens—must be done in tandem.

The various types of detectors used in GC analysis influence the test's sensitivity. Flame ionization detectors are conventional and will detect any organic substance. Nitrogen-phosphorus detectors are particularly useful for detecting halogens (chlorine), or nitrogen- or phosphorus-containing compounds. The nitrogen-phosphorus detector response may be 15 to 300 times greater than that of the flame ionization detector for such compounds—cocaine or phencyclidine. Electron capture detectors are also more sensitive, but their use is restricted to compounds (or derivatives) that contain halogens. A flame ionization detector can measure in 1 ml of urine microgram to submicrogram quantities of drug. For particular cases where sensitivity appears inadequate, or if the drug lacks volatility, the drug may need to be chemically altered before being injected into the column.[25] The sensitivity of gas chromatography at least equals and sometimes betters that of the immunoassays, depending on the choice of detector. Clearly, GC sensitivity varies with the specific techniques and equipment employed.

GC-MS uses a mass spectrometer as a detector. It combines the separating capabilities of GC with the sensitivity and specificity of a mass selective detector. In mass spectrometry, compounds (drugs, molecules) undergo ionization to create various-sized fragments. Filtering these fragment ions through electrostatic or magnetic fields, producing what is called a "mass spectrum," permits identification by their mass-to-charge ratio. Every given compound or drug possesses a unique mass spectrum. Reference libraries of mass spectral data are available for identifying unknowns. The ability of GC-MS to couple spectral data with retention time data offers a definitive identification of drugs and affords GC-MS its deserved reputation as the "gold standard" for confirmatory testing. (HPLC, as discussed later, is also a powerful tool when used with a mass spectrometer.)

GC-MS can be operated in two modes. Used when drugs are of sufficiently high concentrations in the urine, the "full scan" mode produces a complete mass spectrum or "fingerprint" of the drug. Operating in the scan mode, GC-MS has a sensitivity comparable to that of conventional GC—that is, where flame ionization or nitrogen-phosphorus detectors are used. The mass spectrometer can also be operated in the selected ion monitoring mode. In this mode, only a few ion fragments characteristic of the drug are monitored. Because the detector spends more time looking for a few ions, the sensitivity increases about tenfold to 100-fold when compared with the "scan" mode. Some specificity is sacrificed because identification is based on a less specific pattern. The combination, however, of a positive immunoassay and a GC-MS result with the proper retention times and three mass ions of the proper intensities will distinguish the compound in question from more than a million other organic compounds.

In high-performance liquid chromatography, which is not as widely used as gas chromatography, the drug equilibrates in a column between two liquid phases.[25] HPLC, too, may use various detectors, including ultraviolet, fluorescent, electrochemical, diode array scanning, or mass spectral. It is also labor-intensive and requires sample preparation as in GC. HPLC, however, can analyze polar compounds that prove unsuitable for GC without being chemically altered. HPLC has found use in the analysis of benzodiazepines, opiates, and tricyclic antidepressants.[32,33] The sensitivity will depend on the particular drug to be analyzed and the choice of detector, but, in general, HPLC also detects microgram to submicrogram levels per milliliter of urine.

Many laboratory facilities are not equipped to do such sophisticated analyses as gas chromatography, HPLC, and mass spectrometry. The instruments are costly to acquire and maintain and complex to run. Analysts must possess a high level of skill and experience with the extraction procedures, in operating the instrument, and in interpreting the data.

An encouraging recent report on the status of drugs-of-abuse testing showed that laboratories can exhibit great accuracy if appropriate screening, confirmatory tests, and threshold values are used.[34] In this study, 47 laboratories were assessed for their accuracy in detecting five drugs of abuse, including opiates, cannabinoids, amphetamines, cocaine, and phencyclidine. The laboratories in the study did both screening and confirmatory testing of all five drug classes, and they were challenged to detect drugs at concentrations at which they normally accept business. The overall accuracy was better than 95%, with a false-negative rate of 0.8% and a false-positive rate of 0.05%.

It is important that clinicians know whether a laboratory does confirmatory testing or preliminary screening only. The specific threshold concentrations used to report positive tests, as well as policies for reporting positive tests detected below these threshold concentrations, should also be known. Such information and the selection of a laboratory involved in an external proficiency testing program will help ensure reliable drug testing.

Clinical Applications

Over the past 20 years, most of the relatively small number of studies that have examined the clinical applica-

tions of urine screening have taken place in methadone maintenance clinics. Patients on a methadone regimen, though mainly primary opiate abusers, will also abuse other drugs such as cocaine[35] and benzodiazepines[36] in addition to heroin. Despite the high prevalence of illicit drug use in this population, many methadone clinics have remained in a quandary over how best to use the positive urine screening reports they receive.[30]

Several studies indicate that merely confronting drug abusers with the objective evidence of their drug use—in the form of urine screening results—has a negligible impact on drug use. For example, in a study cited above,[30] 76 methadone-maintained patients gave weekly random urine specimens that were tested by TLC. Of these patients, 37 also had their urine screened by EIA. EIA had twice the power of detecting illicit opiate use, but over 13 weeks the EIA group displayed illicit drug usage equivalent to the TLC-only group. Thus, a better capability of objectively discovering illicit drug use produced no alteration in this behavior.

Another study confirmed this impression by observing 431 methadone-maintained patients over a year's time.[37] The patients were randomly assigned to a weekly urine-monitored or a totally unmonitored program. Surprise, spot urine specimens obtained from all subjects at various points in the study indicated that no differences in illicit drug use existed between the two groups.

Only one published study has examined the efficacy of urine surveillance by a controlled trial in a non-methadone treatment setting. The patients were primarily opiate or barbiturate abusers. A total of 29 subjects received hospital detoxification before being randomly assigned to one of three treatment groups: outpatient psychotherapy, group or individual, with weekly urinalysis; outpatient psychotherapy without urinalysis; or a waiting list for outpatient treatment. The patients in the weekly urinalysis group were confronted with their detected drug use in therapy sessions. The study ran for three months. By self-report, the urinalysis group decreased their barbiturate use compared with the other groups. More opiate abuse occurred in the urinalysis group than in the non-urinalysis group, however, though this difference did not attain statistical significance. Even these authors conclude that urine surveillance was merely "somewhat helpful" but would have maximal impact if results were "used in some meaningful program contingency."[38]

Other investigators have adopted this notion of contingencies based on the theory that most patients will refuse to relinquish readily the compulsive use of any potently reinforcing drug. Thus, punishments or rewards more powerful than such reinforcing drugs as heroin or cocaine must be used to induce drug abusers to desist from taking drugs. The best verification to date of this concept comes in the form of a study that involved randomly assigning 69 methadone-maintained patients to a "structured" or "unstructured" treatment.[39] Supervised collecting of urine specimens from all patients was done weekly. Repeated positive urine screens led to methadone detoxification for the structured treatment group. The unstructured treatment group received a notification of concern but no specific consequences for positive urine screening. Over a year's time, the former group used fewer illicit drugs and had a superior degree of retention in treatment compared with the latter group.

Stitzer and colleagues over the years have shown in numerous controlled studies that contingent rewards—cash payments, an increase in methadone dosage, extra take-home methadone—for drug-free urine specimens can reduce illicit benzodiazepine, multiple drug, and opiate abuse in methadone patients.[40-42]

At present, not a single scientific study convincingly indicates that urine screening results used in counseling or confrontation motivate most drug abusers to alter their habits. In contrast, experimental data strongly suggest that, in combination with assured punishments for continued drug use—or rewards for abstinence—urine screening becomes a behavioral strategy successful in treating many drug abusers.

The optimal means of establishing and implementing contingencies for illicit drug use remain uncertain, but open trials of a technique called "contingency contracting" point out possibilities to explore. This technique consists of using a written, detailed, personalized contract specifying the precise consequences that a drug abuser will suffer if he or she provides a given number of positive urine specimens. One uncontrolled, open trial used contingency contracting to treat cocaine abusers.[43] Contracts were offered to 67 patients, of whom 32 agreed to contracts that included urine monitoring and exceedingly aversive consequences—such as notifying an employer of the drug use—for the first cocaine-positive urine specimen. Of those accepting contracts, 31 abstained from using cocaine for the length of the mutually agreed on treatment, with 81% remaining for at least three months. Of the 35 refusing contracts, only 9% (3) stayed in treatment and abstained for four weeks. The longest any of the latter group stayed was two months.

One of the authors also looked at contingency contracting with 17 drug-abusing health care professionals.[44] Again, written contracts mandated a severe consequence—loss of professional license—for a single positive urine screening test. Only two persons had their licenses revoked.

Another open trial exploited contingency contracting to treat 21 methadone-maintained patients considered "treatment failures" based on illicit drug use detected by at least 50% positive weekly urine screens over a 60-day period.[45] These patients had no response to any other treatment method before being placed on written contracts specifying methadone detoxification and discharge for any positive urine screens over a 30-day duration. Of the 21 patients, 11 significantly reduced their illicit drug abuse over the span of the contract and over a 60-day follow-up period. Our own recent work confirmed these findings of an improvement in 50% of methadone treatment failures with contingency contracting and further showed that contingency contracts could be routinely and uniformly applied in the nonresearch setting of a large methadone program.[46] Indeed, contingency contracting has become such an established practice that 72% of methadone clinics nationwide use this technique to manage illicit drug use.[47]

For a clinician treating a drug-abusing patient, some practical issues in regard to implementing contingencies arise. First, it may seem incongruous that any patients would submit to agreements that might result in undesirable or unpleasant consequences. Certainly many will not, but others, if approached during a properly chosen interlude of personal anguish or social duress, will mobilize the remaining shreds of their self-respect to place themselves within the bonds of an agreement that will ultimately help to salvage that self-respect. With the terms of the contract immediately codified in writing and signed by the patient, an external object is

created that directly symbolizes to the patient his or her self-respect. The likelihood of chafing against its restrictions is diminished, permitting an appreciation of the support and protection it provides.

A second issue involves what kinds of negative reinforcers to include in a contract. Certainly these must be individually tailored for each patient, but several general areas apply to many people. Crowley[43,44] has suggested that an agreement focus on a person's means of earning a livelihood, such as notifying an employer or professional licensing board if urine screens remain positive. Often less severe consequences may seem appropriate. Among these might be a patient's agreement to be admitted to hospital after a specified number of positive urine screens. Alternatively, the patient might be required to donate a given sum of money to a specified charitable organization for every positive urine screen. In many cases, a patient's family may involve themselves in the contract process, and a temporary marital separation or a temporary eviction of the patient from the home could be the consequence for positive urine screening, with eventual reunion possible after a string of consecutively negative urine screens. Perhaps the most potentially punitive consequence of all would be reporting a patient's continuing drug use to the criminal justice system if that person has already been embroiled in legal difficulties. Future research may elucidate which of these reinforcers or combination of reinforcers works best for which patients.

Finally, many clinicians may feel uneasy enforcing such seemingly draconian measures as treatment expulsion, loss of income, forced hospital admission, loss of family, or incarceration. One must bear in mind that these contingencies forecast precisely the consequences that would ensue in any event from continued drug use as the addict becomes too destabilized to attend treatment or work regularly, must be admitted for the medical complications of drug use, alienates his or her family, or engages in illegal activities to finance drug purchases. Confronting drug abusers at the outset with the predictable results of their behavior may serve to prevent these consequences rather than make them inevitable.

Conclusion

With all the foregoing in mind, it is possible to formulate some general caveats about urine drug screening in clinical practice. A guiding principle is to maintain an awareness of all three steps in the urine screening process—collection, laboratory analysis, and clinical application—and how they intersect. Thus, collection timing and frequency depend on the clinical situation, including the types of drugs a patient may be abusing and the patterns of abuse. They also depend on what type of laboratory analyses are being done: More sensitive laboratory techniques may permit a less frequent collection schedule. Clinicians must obtain information about a specific laboratory that handles the specimens. Not only must clinicians know which laboratory techniques are used, but they must also have some sense of a particular laboratory's reliability at executing these techniques. This knowledge may help to explain possible false-positives or -negatives that fail to fit the clinical features of a case. Because all laboratories are sometimes fallible, and many are frequently so, it remains incumbent on a laboratory to confirm positive results by a different technique and on clinicians to avoid placing too much clinical weight on the results from any single specimen. In specific clinical situations in which the precise timing of drug use or exceptional accuracy are required, a clinician may need to ask the laboratory to use a specified technique or to send the specimen to another facility that can.

A crucial concept in the clinical arena is the frequent failure of urine monitoring and counseling to help drug-abusing patients curtail their addictions. Obtaining a patient's agreement to participate in a urine monitoring program with specified written consequences for positive urine screens may prove an invaluable maneuver in this context.

In a time of escalating drug abuse and the societal concerns it has raised, practitioners will be increasingly called on to evaluate drug-abusing patients and so to order and interpret urine drug screens. Many practitioners, especially those in areas where no drug abuse programs are available, may find themselves treating drug addiction. While much work remains to be done in developing effective treatments for substance abuse, we have attempted to consolidate and make useful the existing knowledge about urine screening that will continue to gain in importance as one of our effective treatment modalities.

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Medical Practice Opinion

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Commission on Quality Care Review of the California Medical Association. The opinions offered are based on training, experience, and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions, or policy statements.*

Pelvic Lymph Node Dissection and Radical Prostatectomy

QUESTION:

Is it accepted urologic practice to stage a pelvic lymph node dissection, with permanent section microscopic analysis, as a separate operation before doing a radical prostatectomy?

OPINION:

The Scientific Advisory Panel on Urology recognizes that there are two medically accepted procedures for performing pelvic lymph node dissection in patients having radical prostatectomy.

Because it is well documented that 10% to 20% of frozen section assays are false-negative—depending on the institution reporting the data—some urologists prefer to stage pelvic lymph node dissection as a separate operation and await the results of permanent section microscopic analysis before proceeding with radical prostatectomy. Other surgeons rely on frozen section assays at the time of dissection to allow immediate prostatectomy, if the lymph nodes are free of disease.

The choice of procedure should be at the surgeon's discretion, taking into account the variables that may exist within individual patients and institutions.

Approved: May 1988

This opinion has been prepared by the CMA Scientific Advisory Panel on Urology based on available information. It is only an advisory opinion and should not be construed as binding on any individual or as expressing an absolute standard of medical practice. Medical opinion may vary regarding the appropriateness of a particular treatment or service in a given situation. Differences in an individual case should be reviewed by physician medical advisors. Differences of opinion between a medical advisor and attending physician should be referred to the county medical society where the physician practices.